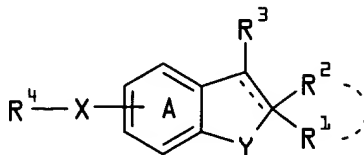


### Version with Markings to Show Changes Made

1. A compound of the formula:



wherein  $R^1$  and  $R^2$  each [represents an aliphatic] represent an acyclic hydrocarbon group, a cycloalkyl group, or  $R^1$  and  $R^2$  form, taken together with the adjacent carbon atom, a 3- to 8-membered carbo or heterocyclic ring which may be substituted;

$R^3$  represents an aromatic group which may be substituted;

$R^4$  represents (1) an aromatic group which may be substituted, (2) an aliphatic hydrocarbon group substituted by an aromatic group which may be substituted, which hydrocarbon group may be further substituted or (3) an acyl;

X and Y each represents an oxygen atom or a sulfur atom which may be oxidized;

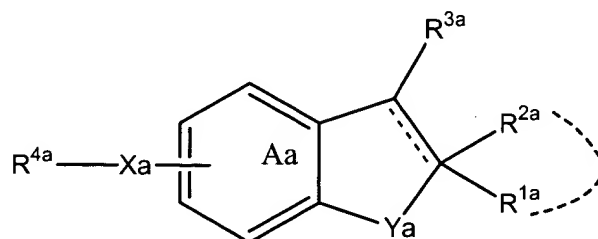
---- represents a single bond or a double bond; and

ring A represents a benzene ring which may be further substituted apart from the group of the formula:  $-X-R^4$  wherein each symbol is as defined above,

provided that when X and Y are oxygen atoms and ---- is a single bond,  $R^4$  is not an acyl, or a salt thereof.

13. A compound of Claim 1 which is **[3-(4-isopropylphenyl)-5-(4-methoxybenzyloxy)-2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran,]** 3-(4-isopropylphenyl)-2,4,6,7-tetramethylbenzofuran-5-yl 4-methoxybenzoate, 3-(4-isopropylphenyl)-5-(4-methoxybenzyloxy)-2,4,6,7-tetramethylbenzofuran, 3-(4-isopropylphenyl)-5-(4-methoxybenzyloxy)-1',4,6,7-tetramethylspiro(benzofuran-2(3H), 4'-piperidine), or a salt thereof.

22. A method for suppressing [neurodegeneration]  $\beta$ -amyloid toxicity in a mammal, which comprises administering to said mammal an effective amount of a compound of the formula:



wherein  $R^{1a}$  and  $R^{2a}$  each represents a hydrogen atom or a hydrocarbon group which may be substituted, or  $R^{1a}$  and  $R^{2a}$  form, taken together with the adjacent carbon atom, a 3- to 8-membered carbo or heterocyclic ring which may be substituted;

$R^{3a}$  represents a hydrogen atom, a lower alkyl which may be substituted or an aromatic group which may be substituted;

$R^{4a}$  represents an aromatic group which may be substituted, an aliphatic hydrocarbon group which may be substituted or an acyl;

Xa represents an oxygen atom or a sulfur atom which may be oxidized;

Ya represents an oxygen atom, a sulfur atom which may be oxidized or an imino which may be substituted;

--- represents a single bond or a double bond;

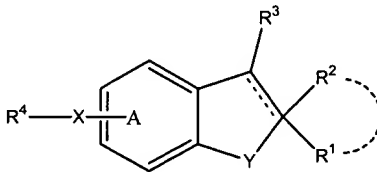
ring Aa represents a benzene ring which may be further substituted apart from (i) the group of the formula:  $-Xa-R^{4a}$  wherein each symbol is as defined above, and (ii) an amino which may be substituted,

provided that when Xa and Ya are oxygen atoms and --- is a single bond,  $R^{4a}$  is not an acyl,

or a pharmaceutically acceptable salt thereof

with a pharmaceutically acceptable excipient, carrier or diluent.

25. A method for suppressing [neurodegeneration]  $\beta$ -amyloid toxicity in a mammal, which comprises administering to said mammal an effective amount of a compound of the formula:



wherein  $R^1$  and  $R^2$  each [represents an aliphatic hydrocarbon group] represent an acyclic hydrocarbon group, a cycloalkyl group, or  $R^1$  and  $R^2$  form, taken together with the adjacent carbon atom, a 3- to 8-membered carbo or heterocyclic ring which may be substituted;

$R^3$  represents an aromatic group which may be substituted;

$R^4$  represents (1) an aromatic group which may be substituted, (2) an aliphatic hydrocarbon group substituted by an aromatic group which may be substituted, which hydrocarbon group may be further substituted or (3) an acyl;

X and Y each represents an oxygen atom or a sulfur atom which may be oxidized;

----- represents a single bond or a double bond;

and Ring A represents a benzene which may be further substituted apart from the group of the formula:  $-X-R^4$  wherein each symbol is as defined above,

provided that when X and Y are oxygen atoms and ----- is a single bond,  $R^4$  is not an acyl,

or a salt thereof

with a pharmaceutically acceptable excipient, carrier or diluent.

26. A method of claim 25, which is a method for [suppressing  $\beta$ -amyloid toxicity] treating Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's chorea or diabetic neuropathy.

28. A method of claim 22, which is a method for [suppressing  $\beta$ -amyloid toxicity] treating Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's chorea or diabetic neuropathy.

## REMARKS

### **I. Claim Amendments**

Applicants acknowledge the allowability of claim 24.

Claims 1 and 25 have been amended to more clearly point out the specific elements of the claimed invention, and to better identify the specific substituents referred to therein.

Claim 13 has been amended to remove the species which is also the subject matter of allowed claim 24.

Claims 22, 25, 26 and 28 have been amended to more clearly point out the specific elements of the claimed invention; while claims 27 and 29 have been canceled.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached pages are captioned "Version with Markings to Show Changes Made".

No amendment of inventorship is necessitated by these amendments.

### **II. Discussion of the Rejection of Claims 1-3, 5-15 and 22 under 35 U.S.C. Sec. 112, First Paragraph**

Claims 1-3, 5-15 and 22 have been rejected under 35 U.S.C. Sec. 112, first paragraph. The Examiner stated that the specification does not reasonably provide enablement for all of the permutations and combinations covered by R<sup>1</sup> and R<sup>2</sup> coming together to form a 3- to 8-membered carbocyclic or heterocyclic ring.

Applicants would like to direct the Examiner's attention to Examples 30-33, found on pages 99-102 and 105 of the specification, wherein spiro compounds representative of the compounds wherein R<sup>1</sup> and R<sup>2</sup> are linked as set forth in claim one as amended, and claim 22 as amended are disclosed. As claims 2, 3 and 5-15 are dependent upon claim 1, Applicants submit that the more specific dependent claims are also adequately enabled. As each of the rejected claims are indeed enabled by the specification, Applicants respectfully request withdrawal of the Sec. 112, first paragraph rejection.

**III. Discussion of the Rejection of Claims 22, 25, 27 and 29 under 35 U.S.C. 112,  
First Paragraph**

Claims 22, 25, 27 and 29 have been rejected under 35 U.S.C. Sec. 112, first paragraph. The Examiner stated that the specification does not provide enablement for the method of treating all diseases related to neurodegeneration.

By this amendment, Applicants have directed claims 22 and 25 to methods for suppressing cell toxicities caused by  $\beta$ -amyloid protein. This amendment introduces no new matter, as support for this amendment is found in the specification at page 1, line 7 *inter alia*. Claim 26 (dependent upon claim 25) and claim 28 (dependent upon claim 22) have been limited to specific diseases, while claims 27 and 29 have been canceled. Support for the specific diseases set forth in claims 26 and 28 as amended is found on page 64, lines 19-25 of the specification, *inter alia*. Therefore, Applicants respectfully request withdrawal of the Sec. 112, first paragraph rejection.

**IV. Discussion of Rejection of Claims 1-3, 5-15 and 22 under 35 U.S.C. Sec. 112,  
First Paragraph**

Claims 1-3, 5-15 and 22 have been rejected under 35 U.S.C. Sec. 112, first paragraph as allegedly lacking description for the new subgenus. By this amendment, Applicants have replaced the phrase "aliphatic hydrocarbon group" with acyclic hydrocarbon group, cycloalkyl group" for the description of  $R^1$  and  $R^2$  in claim 1. This amendment introduces no new matter into the specification, as support for the amendment is found on page 27, line 31- page 28, line 3 of the specification *inter alia*. By this amendment, the hydrocarbon option for substituents  $R^1$  and  $R^2$ , as defined in the claim as originally filed, has been limited only in terms of cyclic substituents, eliminating aromatic groups.

Moreover, the tables on pages 103-105 of the specification illustrate specific compounds which are exemplary of those set forth in independent claims 1 and 22 as amended. As claims 2, 3 and 5-15 depend from claim 1, Applicants submit that the more specific dependent claims are also adequately enabled.

Therefore Applicants respectfully request withdrawal of the 35 U.S.C. Sec. 112, first paragraph rejection.

**V. Conclusion**

Reconsideration of the claims as amended and early allowance of the claims is requested.

Should the Examiner believe that a conference with applicants' attorney would advance prosecution of this application, she is respectfully requested to call applicants' attorney at (847) 383-3391.

Respectfully submitted,

Dated: July 9, 2001

(847)383-3372

(847)383-3391

Elaine M. Ramesh

Mark Chao, Ph.D., Reg. No. 37,293

Elaine M. Ramesh, Ph.D., Reg. No. 43,032

Attorney for Applicants

Customer No. 23115

Takeda Pharmaceuticals North America, Inc.  
Intellectual Property Department  
Suite 500, 475 Half Day Road  
Lincolnshire, IL 60069 USA

**Certificate of Mailing under 37 CFR 1.10**

The undersigned hereby certifies that this document, along with any attachments, is being deposited in an envelope addressed to The Commissioner of Patents and Trademarks, with sufficient postage with the United States Postal Service EXPRESS MAIL Post Office to Addressee Service on this date July 9, 2001

Express Mail Label No. EL 792688517 US

Gail L. Winokur  
Printed Name: Gail L. Winokur